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Award Number: DAMD17-96-C-6105

TITLE: Treatment of Metastatic Breast Carcinoma Refactory to Doxorubicin with Liposomal-Annamycin

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REPORT DATE: October 1999

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	October 1999	Annual (23 Sep 98 - 22 Sep 99)

4. TITLE AND SUBTITLE
Treatment of Metastatic Breast Carcinoma Refactory to Doxorubicin with Liposomal-Annamycin

5. FUNDING NUMBERS
DAMD17-96-C-6105

6. AUTHOR(S)
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 Words)*

Fourteen patients with metastatic breast carcinoma refractory to doxorubicin were entered in a Phase II study of liposomal-annamycin, a new anthracycline antibiotic which has shown ability to circumvent multidrug resistance. A total of 25 doses of liposomal-annamycin were given at three different dose levels. Toxicity was mild and limited to granulocytopenia in less than 50% of patients. No antitumor responses were seen.

14. SUBJECT TERMS
Breast Cancer

15. NUMBER OF PAGES
7

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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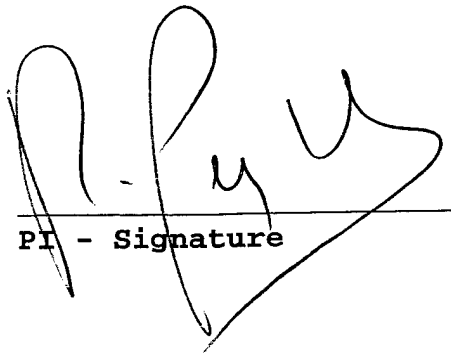

10-19-94

PI - Signature Date

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INTRODUCTION

Liposomal-Annamycin is a liposome entrapped new anthracycline antibiotic which has shown lack of cross-resistance in vitro and in vivo in different cell lines that express P-glycoprotein and MRP. In a Phase I study conducted in patients with solid tumors, the dose limiting toxicity was myelosuppression. No alopecia, mucositis, cardiac, skin, nor gastrointestinal toxicities were observed. The maximum tolerated dose was 210 mg/m^2 administered intravenously every 3 weeks. Because the multidrug resistance phenotype has been associated with some human malignancies, particularly acute leukemia and breast carcinoma, when they become refractory to standard chemotherapy, we proposed and initiated a Phase II study of liposomal-Annamycin in patients with metastatic breast carcinoma refractory to doxorubicin. This report summarizes the status of this study.

REPORT

Because of a transfer of the PI to New York University Medical Center, work during the last period of support was very limited. An extension of one year will be needed and requested to complete this project.

ELIGIBILITY CRITERIA

1. Metastatic breast carcinoma
2. Anthracycline-resistant
3. Measurable disease
4. Life expectancy >12 weeks
5. Prior anthracycline <350 mg/m^2 of doxorubicin equivalent by bolus, <450 mg/m^2 by prolonged infusion
6. Adequate bone marrow function
7. Ejection fraction >55%

PATIENT CHARACTERISTICS

A total of fourteen patients have been entered in the study and a total of 25 doses of liposomal-annamycin have been given. The following Table summarizes the characteristics of the patients entered.

Number of patients entered	14
Number of patients evaluable	14
Age median (range)	50 (34-73)
Performance status	

1	12
2	2
Sex: female	14
Race:	
Black	7
Hispanic	3
White	4
Histology	
Ductal carcinoma, invasive	14
Prior therapy	
Chemotherapy	14
Hormonal therapy	3
Radiation therapy	6
Surgical therapy	7
Prior chemotherapy: number of regimens	
1	2
2	2
3	8
4	2
number of agents	
3	1
>3	13

TOXICITY

Toxicity has been mild and mostly limited to granulocytopenia as indicated below:

1. Myelosupression (first 9 patients)

Dose	No courses	Granulocyte nadir (range) (day)	Platelet nadir (range) (day)
190mg/m^2	4	1.2 (0.7-1.8) 11	192 (134-251) 14
210	8	1.5 (0.5-3.0) 15	218 (145-288) 10

250	2	0.8 (0.3-1.3) 11	169 (146-192) 8

2. Non-hematological toxicities

Nausea and vomiting was observed after 6 courses (grade 3 in one, grade 2 in two, and grade 1 in three). Diarrhea grade 1 was observed after one course. Stomatitis was observed after 4 courses (grade 2 in two, and grade 1 in two). One grade 1 allergic reaction was observed.

ANTITUMOR ACTIVITY

Fourteen patients progressed after 1 or 2 cycles of liposomal-annamycin. One patients remained stable after 2 cycles of liposomal-annamycin. No tumor responses have been seen so far.

CORRELATIVE TISSUE STUDIES

Three tissue specimens were obtained pre-therapy for MDR analysis. These samples are kept frozen in Dr. Sahin's laboratory and will be assayed when the study is completed and/or responses are seen.

CONCLUSIONS

Results obtained to date suggest that liposomal-annamycin is very well tolerated with grade 3 granulocytopenia being observed in a minority of patients. Non-hematological toxicity is minimal.

No tumor responses have been observed so far.

The study will continue to complete fourteen fully evaluable patients. Baseline tumor biopsies will be obtained to analyze MDR status. Because no responses have been seen in this cohort of 14 patients, further accrual is restricted to patients with MDR ⊕ tumors.

REFERENCES

1. Booser D, Zou Y, Priebe W, Perez-Soler R. Phase I clinical and pharmacology study of liposomal-annamycin. In preparation for submission to Clinical Cancer Research.
2. Booser D, Esparza-Guerra L, Zou Y, Priebe W, Perez-Soler R. Liposomal-annamycin. Phase I clinical and pharmacological study. Proceed. ASCO 16:762 p217a, 1997.